Exhibit B

USPTO PATENT FULL-TEXT AND IMAGE DATABASE

Searching 1976 to present...

Results of Search in 1976 to present db for:
ACLM/"small molecule$": 157 patents.
*Hits **1** through **50** out of **157***

Next 50 Hits

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Refine Search ACLM/"small molecule$"

	PAT. NO.	Title
1	6,589,773	Methods and compositions for a modified yeast strain with increased permeability and uses thereof
2	6,579,725	Linkers for synthesis of oligosaccharides on solid supports
3	6,579,696	Polymyxin B conjugates
4	6,566,805	Organic electro-luminescent device with first and second composite layers
5	6,566,406	Biocompatible crosslinked polymers
6	6,566,086	Diagnostic kit for detecting creatine levels
7	6,555,360	Flow injection flow cytometry system for on-line monitoring of biroreactors and method for monitoring
8	6,552,093	Compositions containing particles of highly fluorinated ion exchange polymer
9	6,544,334	Systems and methods for the deposition and curing of coating compositions
10	6,541,580	Atom or group transfer radical polymerization
11	6,533,912	Increased throughput analysis of small compounds using multiple temporally spaced injections
12	6,518,480	Selective target cell activation by expression of a G protein-coupled receptor activated superiorly by synthetic ligand
13	6,509,162	Methods for selectively modulating survivin apoptosis pathways
14	6,503,717	Methods of using randomized libraries of zinc finger proteins for the identification of gene function
15	6,500,628	Nucleic acid molecules encoding human kinase and phosphatase homologues and uses therefor
16	6,489,304	Hyperstructure-forming carriers

17 6,486,601 Organic luminescence device with reduced leakage current
18 6,486,151 N-oxides of heterocyclic esters, amides, thioesters, and ketones
19 6,485,884 Method for patterning oriented materials for organic electronic displays and devices
20 6,482,603 Method of detecting drug-receptor and protein-protein interactions
21 6,482,564 Electronically active primer layers for thermal patterning of materials for electronic devices
22 6,482,346 Method for manufacturing an in-mold display
23 6,468,755 Method for identifying compounds for treatment of insulin resistance
24 6,461,331 Device and method for infusion of small molecule insulin mimetic materials
25 6,455,074 Methods for fabricating polymer-based controlled release devices
26 6,451,524 Identification of disease predictive nucleic acids
27 6,440,668 Method of DNA shuffling with polynucleotides produced by blocking or interrupting a synthesis or amplification process
28 6,435,012 Method for determination of chromatographic media parameters in packed beds of hydrophobic polymer particles
29 6,429,191 Treatment of hearing impairments
30 6,420,563 Small molecule modulators of G protein-coupled receptor six
31 6,417,209 Heterocyclic ketone and thioester compounds and uses
32 6,416,738 Pretargeting methods and compounds
33 6,413,717 Methods for indentifying anti-cancer agents
34 6,410,201 Thermal transfer element and process for forming organic electroluminescent devices
35 6,391,572 Methods for identifying modulators of transcriptional activator protein interactions
36 6,387,645 Methods and materials relating to novel CD39-like polypeptides
37 6,387,641 Crystallized P38 complexes
38 6,384,208 Sequence directed DNA binding molecules compositions and methods
39 6,379,853 Electrophotographic imaging member having two charge transport layers for limiting toner consumption
40 6,377,895 Method for planning the generation of combinatorial chemistry libraries method for planning the generation of combinatorial chemistry libraries
41 6,377,346 Sample imaging device
42 6,358,697 Intracellular pharmaceutical targeting
43 6,358,664 Electronically active primer layers for thermal patterning of materials for electronic devices
44 6,355,163 Apparatus for screening compound libraries
45 6,346,389 Method for selectively modulating the interactions between survivin and tubulin
46 6,344,318 Methods of producing nucleic acid ligands
47 6,342,495 Agonists and antagonists of peripheral-type benzodiazepine receptors
48 6,339,100 Methods for inhibiting mastocytosis
49 6,337,181 Method of specifying vaccine components for viral quasispecies
50 6,337,102 Low pressure vapor phase deposition of organic thin films

United States Patent **6,020,096**
Fuller , et al. **February 1, 2000**

Charge transport layer and process for fabricating the layer

Abstract

An electrophotographic imaging member comprising a charge generating layer comprising trigonal selenium particles and a charge transport layer, the charge transport layer including a protonic acid or Lewis acid, a charge transporting small molecule, a film forming polymer, and polyalkylene-block-polyethylene oxide. This imaging member may be fabricated using a suitable solvent for applying the charge transport layer.

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Assignee: **Xerox Corporation** (Stamford, CT)

Appl. No.: **181451**

Filed: **October 28, 1998**

Current U.S. Class: **430/58.35**; 430/132

Intern'l Class: G03G 005/087

Field of Search: 430/58.35,127,132

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5863685	Jan., 1999	DeFeo et al.	430/132.
5882831	Mar., 1999	Fuller et al.	430/132.

Primary Examiner: Goodrow; John

Claims

What is claimed is:

1. An electrophotographic imaging member comprising a charge generating layer comprising trigonal selenium particles and a charge transport layer, the charge transport layer comprising

a protonic acid or Lewis acid,

a charge transporting ***small molecule,***

a film forming polymer, and

polyalkylene-block-polyethylene oxide.

2. An electrophotographic imaging member according to claim 1 wherein the film forming polymer is a polycarbonate.

3. An electrophotographic imaging member according to claim 1 wherein the charge transport layer comprises between about 10 ppm and about 150 ppm by weight of polyalkylene-block-polyethylene oxide, based on the weight of the film forming polymer.

4. An electrophotographic imaging member according to claim 1 wherein the charge transport layer is formed from a coating solution comprising the acid, charge transporting ***small molecule,*** film forming polymer, polyalkylene-block-polyethylene oxide and a solvent, the solvent comprising methylene chloride and the acid comprising 5 ppm and about 20 ppm by weight of trifluoroacetic acid, based on the weight of the solvent.

5. An electrophotographic imaging member according to claim 1 wherein the charge transport layer comprises between about 30 and about 60 percent by weight of the charge transporting ***small molecule,*** based on the total weight of the dried charge transport layer.

6. An electrophotographic imaging member according to claim 1 wherein the charge transporting ***small molecule*** comprises an aromatic amine compound.

7. An electrophotographic imaging member according to claim 1 wherein the charge transport layer comprises between about 40 and about 70 percent by weight of the film forming binder, based on the total weight of the dried charge transport layer.

8. An electrophotographic imaging member according to claim 1 wherein the polyalkylene-block-polyethylene oxide is represented by the formula:

A--B (I)

wherein A is represented by the formula: ##STR6## wherein R and R.sub.1 are

independently selected from hydrogen and an alkyl group having 1 to about 10 carbon atoms; and

x is a number of 1 to about 142 and

B is represented by the formula: ##STR7## wherein R.sub.2 is selected from the group consisting of hydrogen and an alkyl group having 1 to about 5 carbon atoms, and

y is a number of from about 2 to about 817.

9. An electrophotographic imaging member according to claim 1 wherein the charge transporting layer comprises at least about 10 ppm polyalkylene-block-polyethylene oxide, based on the weight of the film forming polymer.

10. A process for fabricating an electrophotographic imaging member comprising providing a charge generating layer comprising trigonal selenium particles, forming a charge transporting layer coating composition to the charge generating layer, the coating composition comprising a charge generating layer and a charge transport layer, the charge transport layer comprising

a protonic acid or Lewis acid,

a charge transporting ***small molecule,***

a film forming polymer,

solvent, and

polyalkylene-block-polyethylene oxide, and

drying the coating to form a charge transporting layer.

11. A process for fabricating an electrophotographic imaging member according to claim 10 wherein charge transporting layer coating composition comprises between about 40 ppm and about 150 ppm of the polyalkylene-block-polyethylene oxide, based on the weight of the film forming polymer.

12. A process for fabricating an electrophotographic imaging member according to claim 11 wherein charge transporting layer coating composition comprises at least about 10 ppm of the polyalkylene-block-polyethylene oxide, based on the weight of the film forming polymer.

13. A process for fabricating an electrophotographic imaging member according to claim 11 wherein the acid in the charge transporting layer coating composition comprises at least about 5 ppm of the trifluoroacetic acid, based on the weight of the solvent.

14. A process for fabricating an electrophotographic imaging member according to claim 13 wherein charge transporting layer coating composition comprises between about 5 ppm and about 20 ppm of the trifluoroacetic acid, based on the weight of the solvent.

15. A process for fabricating an electrophotographic imaging member according to claim 10 wherein the polyalkylene-block-polyethylene oxide is represented by the formula:

A--B (I)

wherein A is represented by the formula: ##STR8## wherein R and R.sub.1 are independently selected from hydrogen and an alkyl group having 1 to about 10 carbon atoms; and

x is a number of 1 to about 142 and

B is represented by the formula: ##STR9## wherein R.sub.2 is selected from the group consisting of hydrogen and an alkyl group having 1 to about 5 carbon atoms, and

y is a number of from about 2 to about 817.

United States Patent **6,010,478**
Bellhouse , et al. **January 4, 2000**

Trans-mucosal particle delivery

Abstract

A needleless syringe capable of accelerating particles comprising a therapeutic agent across skin or mucosal tissue of a vertebrate subject is provided. The syringe comprises an elongate tubular nozzle having a bend along its length and is connected to or capable of connection to a suitable energizing means for producing in the nozzle a supersonic condition sufficient to cause delivery of the particles to a target surface. A method for delivering particles comprising a therapeutic agent from the needleless syringe is also provided.

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Appl. No.: **919184**

Filed: **August 14, 1997**

Foreign Application Priority Data

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Intern'l Class: A61M 005/30

Field of Search: 604/68,70,72,131,130,140,141,143,146 222/631,389

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Primary Examiner: McDermott; Corrine
Assistant Examiner: Gring; Kent
Attorney, Agent or Firm: McCracken; Thomas P.

Parent Case Text

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of International Patent Application Number PCT/GB96/00340, filed Feb. 14, 1996, designating the United States, from which priority is claimed pursuant to 35 U.S.C. .sctn.365(c) and which is incorporated herein by reference in its entirety .

Claims

We claim:

1. A needleless syringe for delivering particles comprising a therapeutic agent across skin or mucosal tissue of a vertebrate subject, said syringe comprising:

(a) an elongate tubular nozzle having an upstream terminus and a downstream terminus

and a bend between said upstream and downstream termini, wherein the upstream terminus is capable of interfacing with an energizing means; and

(b) release means associated with the nozzle for releasing into the upstream terminus of the nozzle an energetic force from the energizing means to create a supersonic condition within the nozzle.

2. The syringe of claim 1, wherein the upstream terminus of the nozzle is interfaced with a source of pressurized gas.

3. The syringe of claim 2, wherein the source of pressurized gas comprises a gas canister containing a releasable volume of a driving gas.

4. The syringe of claim 2, wherein the source of pressurized gas contains a gas which is lighter than air.

5. The syringe of claim 4, wherein the nozzle contains a volume of gas that is lighter than air.

6. The syringe of claim 2 further comprising valve means capable of actuation to release a volume of gas from the source of pressurized gas to create a gaseous shock wave within the nozzle.

7. The syringe of claim 6, wherein the release means comprises a rupturable membrane arranged within and closing the nozzle, whereby the released gas is temporarily retained in a chamber behind said membrane prior to the rupture thereof.

8. The syringe of claim 1, wherein the release means is a self-opening valve.

9. The syringe of claim 1, wherein the nozzle contains a volume of gas that is lighter than air.

10. The syringe of claim 1, wherein the supersonic condition within the nozzle is a supersonic gas flow.

11. The syringe of claim 10, wherein the nozzle diameter between the bend and the downstream terminus is smaller than the nozzle diameter between the upstream terminus and the bend, whereby the supersonic gas flow is attained in the nozzle only between the bend and the downstream terminus.

12. The syringe of claim 11, wherein the portion of the nozzle between the bend and the downstream terminus has a convergent portion.

13. The syringe of claim 1 further comprising an upstream and a downstream rupturable membrane that extend across the interior of the nozzle, wherein particles comprising a therapeutic agent are housed in the nozzle between said rupturable membranes.

14. The syringe of claim 13, wherein the release means comprises the upstream or downstream rupturable membrane.

15. The syringe of claim 1 further comprising a diaphragm arranged adjacent to the downstream terminus of the nozzle, said diaphragm having an internal surface facing the interior of the nozzle and an external surface, wherein said diaphragm is moveable between an initial position in which a concavity is provided on the external surface of the diaphragm, and a dynamic position in which the external surface of the diaphragm is substantially convex.

16. The syringe of claim 15, wherein the diaphragm is an eversible dome-shaped membrane comprised of a flexible polymeric material.

17. The syringe of claim 15, wherein the diaphragm is a bistable membrane that is moveable between an initial inverted position and a dynamic everted position.

18. The syringe of claim 15 further comprising particles comprising a therapeutic agent housed within the concavity in the external surface of the diaphragm.

19. The syringe of claim 1, wherein the nozzle is flexible such that the bend in the nozzle can be adjusted over a range of angles.

20. A method for delivering particles comprising a therapeutic agent to skin or mucosal tissue, said method comprising:

(a) providing the needleless syringe of claim 1 interfaced with an energizing means;

(b) loading said needleless syringe with particles comprising a therapeutic agent;

(c) positioning the downstream terminus of the nozzle of said syringe adjacent to the skin or mucosal tissue; and

(d) actuating the release means to create a supersonic condition within the nozzle, thereby accelerating said particles into the skin or mucosal tissue.

21. The method of claim 20, wherein the particles are accelerated toward the skin or mucosal tissue at a velocity of about 200 to 2,500 m/sec.

22. The method of claim 20, wherein the particles have a size predominantly in the range of about 10 to 40 .mu.m.

23. The method of claim 20, wherein the particles have a density in the range of 0.5 to 2 g/cm.sup.3.

24. The method of claim 20, wherein the particles are accelerated from the downstream

terminus of the nozzle at a momentum density between 4 and 7 kg/sec/m.

25. The method of claim 20, wherein the therapeutic agent is a topically active local anaesthetic.

26. The method of claim 25, wherein the local anaesthetic is selected from the group consisting of lignocaine hydrochloride, lignocaine base, ropivacaine hydrochloride, bupivacaine, procaine, prilocaine, tetracaine, etidocaine, and benzocaine.

27. The method of claim 25, wherein the local anaesthetic is mixed with epinephrine.

28. The method of claim 20, wherein the therapeutic agent is selected from the group consisting of a systemically-active organic ***small molecule,*** an inorganic ***small molecule,*** a peptide, a protein, a vaccine, an oligonucleotide, and a metal ion.

29. The method of claim 28, wherein the therapeutic agent is selected from the group consisting of insulin, testosterone, growth hormone, glucagon, atropine, alprazolam, calcitonin, desmopressin, 5HT, dihydroergotamine, and interleukin.

30. The method of claim 20, wherein the particles are delivered to a mucosal surface.

31. The method of claim 30, wherein the particles are delivered to a mucosal surface selected from the group consisting of gum mucosa, cheek mucosa, palate mucosa, vaginal mucosa, rectal mucosa, nasal mucosa, and ocular mucosa.

Description

TECHNICAL FIELD

The present invention relates generally to a needleless syringe for use in delivery of particles of a therapeutic agent to a target skin or mucosal surface.

BACKGROUND OF THE INVENTION

In commonly owned U.S. Pat. No. 5,630,796, a noninvasive delivery system is described that entails the use of a needleless syringe. The syringe is used for transdermal delivery of powdered therapeutic compounds and compositions to skin, muscle, blood or lymph. The syringe can also be used in conjunction with surgery to deliver therapeutics to organ surfaces, solid tumors and/or to surgical cavities (e.g., tumor beds or cavities after tumor resection).

The needleless syringe is constructed as an elongate tubular nozzle, having a rupturable membrane initially closing the passage through the nozzle adjacent to the upstream end of the nozzle. Particles comprising a powdered therapeutic agent are located adjacent to

United States Patent **5,928,868**
Liu , et al. **July 27, 1999**

Three hybrid screening assay

Abstract

Methods and a kit are provided for characterizing small molecules from a library of small molecules or alternatively identifying protein targets to which known small molecules bind. The methods include forming hybrid ligand in which at least one ligand is a small molecule. The hybrid ligand is introduced into cells that in turn contain a first and a second expression vector. Each expression vector includes DNA for expressing a hybrid protein that encodes a target protein linked to a coding sequence for a transcriptional module. The cells further contains a reporter gene, the expression of which is conditioned on the proximity of the first and second hybrid proteins to each other, an event that occurs only if the hybrid ligand binds to target sites on both hybrid proteins. Those cell which express the reporter gene are selected and the unknown small molecule or the unknown hybrid protein is identified.

Inventors: **Liu; Jun** (Cambridge, MA); **Licitra; Edward J.** (Somerset, NJ)
Assignee: **Massachusetts Institute of Technology** (Cambridge, MA)
Appl. No.: **845674**
Filed: **April 25, 1997**

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Intern'l Class:	C12Q 001/68; C07H 021/04; C12N 015/00
Field of Search:	435/6,69.1,69.4,69.7,70.1,71.1,7.1,29,465,476,483,489

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Primary Examiner: Horlick; Kenneth R.
Attorney, Agent or Firm: Bromberg & Sunstein LLP

Parent Case Text

The present application claims priority from U.S. provisional application No. 60/017,341, filed on Apr. 26, 1996 herein incorporated by reference.

Claims

We claim:

1. A method for identifying which if any ***small molecule*** from a pool of candidate small molecules binds a known first target in a population of cells, comprising:

(a) with respect to each candidate ***small molecule,*** forming a hybrid ligand by chemical linkage of the ***small molecule*** to a known molecule, the known molecule binding a known second target;

(b) introducing each hybrid ligand into the cells, each cell containing;

(i) a first expression vector, including a DNA encoding the known first target, linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector including DNA encoding the known second target, linked to a coding sequence for a second transcriptional module for expression as a second hybrid protein; and

(iii) a third vector including a reporter gene wherein expressing the reporter gene is

conditioned on the proximity of the first and second hybrid proteins;

(c) permitting the hybrid ligand to bind to the first hybrid protein and the second hybrid protein so as to activate the expression of the reporter gene;

(d) selecting which sample expresses the reporter gene; and

(e) identifying the ***small molecule*** that binds the first target.

2. A method according to claim 1, wherein the cells are genetically altered.

3. A method according to claim 1, wherein the cells are eukaryotic cells.

4. A method according to claim 1, wherein the environment in step (b) is s selected from the group consisting of insect cells, yeast cells, mammalian cell, and their lysates.

5. A method according to claim 3, wherein the cells are yeast cells.

6. A method according to claim 3, wherein the cells are mammalian cells.

7. A method according to claim 5, further comprising the step of enhancing the permeability of the yeast membrane.

8. A method according to claim 7, wherein the step of enhancing the permeability of the yeast membrane further comprises selecting yeast mutants having enhanced membrane permeability.

9. A method according to claim 1, further comprising introducing the hybrid molecule into the cells by electroporation.

10. A method according to claim 1, wherein the first and second transcription module of step (b) (i) and (ii) is selected from the group consisting of a DNA binding protein and a transcriptional activator.

11. A method according to claim 1, wherein the pool of candidate small molecules of step (a) is a pool of candidate steroid molecules.

12. A method according to claim 1, wherein the ***small molecule*** is obtained from a combinatorial library.

13. A method according to claim 12, wherein the ***small molecule*** is obtained from a combinatorial library of small organic molecules.

14. A method according to claim 1, wherein the ***small molecule*** is an environmental contaminant.

15. A method according to claim 1, wherein the reporter gene is selected from the group consisting of Lac Z, GFP, luciferase and an antibody coding region.

16. A method according to claim 14, wherein the steps (b)-(e) of the method are iteratively repeated, in the presence of a preparation of random small molecules for competitive binding with the hybrid ligand so as to identify an additional ***small molecule*** capable of competitively binding the first target.

17. A method for identifying a protein target to which a ***small molecule*** is capable of binding, comprising:

(a) providing a hybrid ligand consisting essentially of a first small molecule ligand, identified as ligand A and a second molecule identified as ligand B, that are covalently linked by chemical synthesis, wherein ligand A has a specificity for a first preselected protein target and ligand B has a specificity for a second unknown protein target;

(b) introducing the hybrid ligand into a population of cells, each cell containing;

(i) a first expression vector, including DNA encoding the first protein target for ligand A, linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector including a random DNA fragment encoding the second protein target linked to a second transcriptional module for expression as a second hybrid protein; and

(iii) a third vector including a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(c) permitting the hybrid ligand to bind the first hybrid protein through ligand A and the second hybrid protein through ligand B so as to activate the expression of the reporter gene;

(d) selecting the cells expressing the reporter gene; and

(e) identifying the second protein target in the samples selected in (d).

18. A kit for detecting interactions between pharmacologically relevant small molecules and proteins, comprising;

(a) a preactivated ***small molecule*** ligand A and reagents for forming a hybrid molecule with at least one type of ***small molecule*** ligand B;

(b) a first expression vector including DNA encoding the binding protein for Ligand A linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(c) a second expression vector including a random DNA fragment encoding a polypeptide linked to a coding sequence for a second transcriptional module for expression as a second hybrid protein;

(d) a third vector including a reporter gene wherein transcription of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(e) an environment for transcription and translation of the hybrid proteins and the reporter gene; and

(f) a signal to detect the expression of the reporter gene following the formation of a trimeric complex between the hybrid ligand and the hybrid proteins.

19. A method according to claim 17, wherein the second expression vector of step (b) (ii) contains a random DNA fragment of a size suited for encoding a gene product, wherein the DNA fragment is from a library of DNA.

20. A method according to claim 19, wherein the DNA fragments in the library are selected from the group consisting of genomicDNA, cDNA and syntheticDNA.

21. A method according to claim 17, wherein the DNA fragment of step (b) (ii) is obtained from a plurality of libraries.

22. A method according to claim 20, wherein the cDNA library is derived from an immune cell.

23. A method according to claim 20, wherein the cDNA is derived from an immune cell capable of producing an immune response to the ligand B.

24. A method according to claim 17, wherein ligand B has a known biological function.

25. A method according to claim 17, wherein the population of cells are genetically altered.

26. A method according to claim 25, wherein the cells are eukaryotic cells.

27. A method according to claim 26, wherein the population of cells is selected from the group consisting of insect cells, yeast cells and mammalian cell.

28. A method according to claim 27, wherein the cells are yeast cells.

29. A method according to claim 27, wherein the cells are mammalian cells.

30. A method according to claim 28, further comprising the step of enhancing the permeability of the yeast membrane.

31. A method according to claim 30, wherein the step of enhancing the permeability of the yeast membrane further comprises selecting yeast mutants having enhanced membrane permeability.

32. A method according to claim 17, wherein step (b) further comprises introducing the hybrid ligand into the cells by electroporation.

33. A method according to claim 17, wherein the steps (b)-(e) of the method are repeated iteratively in the presence of a preparation of random small molecules for competitive binding with the hybrid ligand and identifying the ***small molecule*** capable of competitively binding the second hybrid protein.

Description

TECHNICAL FIELD

The present invention relates to a generalized screening method and kit for small molecules that bind selected cellular targets and for targets capable of binding selected small molecules.

BACKGROUND OF THE INVENTION

A fundamental area of inquiry in pharmacology and medicine is the determination of ligand-receptor interactions. The pharmacological basis of drug action, at the cellular level, is quite often the consequence of non-covalent interactions between therapeutically relevant small organic molecules and high affinity binding proteins within a specific cell type. These small organic ligands may function as agonists or antagonists of key regulatory events which orchestrate both normal and abnormal cellular functions. For years the pharmaceutical industry's approach to discovering such ligands has been one of the random screening of thousands of small molecules in specific in vitro and in vivo assays to determine a potent lead compound for their drug discovery efforts. This lead compound often exerts very well-defined effects with regard to cell function (e.g. inhibition of cytokine production or DNA replication) but its mechanism of action at the molecular (ligand-protein interaction) level remains elusive. There is an unmet need for a general and efficient method to identify the cellular targets for these pharmacological agents so as to accelerate the search for novel drugs both at the basic and applied levels of research.

At this time, no efficient methodologies exist for rapidly identifying a biological target such as a protein for a particular small molecule ligand. Existing approaches include the use of affinity chromatography, radio-labeled ligand binding and photoaffinity labeling in combination with protein purification methods to detect and isolate putative target proteins. This is followed by cloning of the gene encoding the target protein based on the